UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte CHARLES W. RITTERSHAUS and LAWRENCE J. THOMAS

Appeal No. 2005-0547
Application No. 09/529,762

ON BRIEF

Before ELLIS, ADAMS, and MILLS, Administrative Patent Judges.

ADAMS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on the appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 40-48, 51 and 52, which are all the claims pending in the application.

Claim 40 is illustrative of the subject matter on appeal and is reproduced below:

40. A method of modulating the level of endogenous cholesteryl ester transfer protein (CETP) activity in a mammal comprising administering to the mammal a whole, non-endogenous CETP in an amount effective to reduce CETP activity below 20% of that of the untreated mammal.

The references relied upon by the examiner are:

Kwoh et al. (Kwoh)	WO 96/39168	Dec. 12, 1996

Stevens et al. (Stevens), USE OF SYNTHETIC PEPTIDES FOR DEVELOPING A VACCINE AGAINST HUMAN CHORIONIC GONADOTROPIN, in SYNTHETIC VACCINES, Vol. II, Ch. 18, pp. 111-33 (Ruth Arnon, ed., CRC Press, Inc. Boca Raton, Florida, 1987)

Breslow, "Transgenic mouse models of lipoprotein metabolism and atherosclerosis," Proc. Natl. Acad. Sci., U.S.A., Vol. 90, pp. 8314-18 (1993)

Marotti et al. (Marotti), "Severe atherosclerosis in transgenic mice expressing simian cholesteryl ester transfer protein," Nature, Vol. 364, pp. 73-75 (1993)

(Kuby) ANTIGENS, in IMMUNOLOGY, Ch. 4, pp. 85-96 (2nd ed., Kuby ed, W.H. Freeman and Co., New York 1994)

Ngo et al. (Ngo), Computational Complexity, Protein Structure Prediction, and the Levinthal Paradox, in The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495 (K. Merz, Jr. et al., eds., Birkhäuser, Boston 1994)

GROUNDS OF REJECTION

Claims 40-48, 51 and 52 stand rejected under 35 U.S.C. § 112, first paragraph, as being based on an insufficient disclosure to enable the full scope of the claimed invention.

Claims 40-48, 51 and 52 stand rejected under 35 U.S.C. § 112, first paragraph, as the specification fails to adequately describe the claimed invention.

Claims 40-45, 47, 51 and 52 stand rejected under 35 U.S.C. § 102(a) as anticipated by Kwoh.

We affirm the rejection under 35 U.S.C. § 102(a) and reverse the rejections under 35 U.S.C. § 112, first paragraph.

DISCUSSION

Enablement:

According to the examiner (Answer, bridging paragraph, pages 3-4), appellants' specification provides an enabling disclosure of a "method compris[ing] administering to a rabbit a C-terminus of human CETP peptide conjugated to tetanus toxoid consisting of SEQ ID NO: 7[,] or a whole recombinant human CETP consisting of SEQ ID NO: 1 ... for reducing CETP activity, increasing the HDL-cholesterol, and lowering LDL-cholesterol associated with atherosclerosis...." Nevertheless, the examiner finds (Answer, page 5), notwithstanding polypeptides having SEQ ID NOs: 1, 3, 5 and 6, appellants' specification fails to provide an enabling disclosure of the claimed methods for, inter alia, the administration of any whole, non-endogenous CETP to any mammal.

In support of this rejection the examiner relies on a number of references. We will take each in turn. The examiner relies (Answer, page 6) on Ngo to teach that guidance is required when modifying a CETP by inter alia, substitution, addition or deletion so that the CETP maintains its original structure/function. According to appellants (Brief, page 14), guidance can be found on page 8, line 22 to page 9, line 17 of the specification. At the cited section of appellants' specification we find two representative examples, using a rabbit and a human CETP. According to appellants' specification, page 9, comparison of human and rabbit CETPs reveals that the rabbit CETP has a 19-amino acid segment from amino acid Ala_{393} through Ala_{411} that does not exist in human CETP.

Accordingly, appellants' specification discloses (id.), the deletion of this 19-amino acid segment in the rabbit CETP would result in a "humanized rabbit CETP." In addition, appellants' specification discloses (id.), there is only one difference between the C-terminal portion of the human and rabbit CETPs – a Lys_{485} of the rabbit CETP corresponds to Glu_{465} in the human CETP. Thus, appellants provide SEQ ID NO: 6, as evidence that Lys_{485} of the rabbit CETP is replaced with a Glu_{465}. Thus, contrary to the examiner's assertion, it would reasonably appear that the specification provides guidance on how to modify a CETP. In this regard, we note that the examiner not only failed to address this portion of appellants' disclosure, but the examiner also failed to explain why a non-endogenous CETP from any source would not be able to function in appellants' claimed method.[1]

The examiner also relies on Kuby to support his assertion that "[i]t is [sic] well known in the art at the time the invention was made that antibody epitopes ... are not linear and are comprised of complex three-dimentional [sic] array[s] of scattered residues which will fold into specific conformation[s] that contribute to binding." Answer, page 6. However, as illustrated by Kuby, the examiner's assertion is technically inaccurate. According to Kuby (page 94), "B-cell epitopes can contain sequential or nonsequential amino acids. Epitopes may be composed of sequential contiguous residues along the polypeptide chain or

[1] In this regard, we are not persuaded by the examiner's assertion (Answer, page 6), "[t]here are no additional human CETP[s] which have been demonstrated to be useful for immunizing any mammal...." To the contrary, the examiner has provided no evidence to suggest that allelic variants of any mammal's endogenous CETP would not be useful in the claimed method.

nonsequential residues from segments of the chain brought together by the folded conformation of the protein." Accordingly, we are not persuaded by the examiner's assertion.

The examiner finds (Answer, page 6), Marotti "[t]each[es] that transgenic mice expressing exogenous simian cholesteryl ester transfer protein (CETP) results in severe atherosclerosis with a marked increases [sic] in the concentration of LDL-cholesterol and a decrease in the concentration of HDL-cholesterol...." However, in our opinion, the examiner has failed to appreciate the context in which Marotti performed the studies. According to Marotti (page 73, column 1), "[t]o evaluate the effect of CETP in the development of atherosclerosis, we produced transgenic C57BL/6 mice that express cynomolgus monkey CETP at various levels." The C57BL/6 mice, however, have little or no CETP activity. Marotti, page 73, second column. Marotti, used three strains of mice for the study (id.), "C57BL/6 mice, which have little or no CETP activity; UCTP-45, a transgenic C57BL/6 mouse expressing simian CETP at relatively low levels; and UCTP-20, a transgenic C57BL/6 mouse expressing CETP at relatively high levels (Table 1)." Thus, consistent with appellants' claims, which are directed at administering non-endogenous CETP as a vaccine[2] to reduce the endogenous CETP activity (e.g., claim 40) resulting in increased HDL levels (e.g. claim 42) and reduced LDL levels (e.g., claim 45), table 1 of Marotti

[2] According to appellants' specification (page 8), the claimed invention is directed "to the control of endogenous CETP activity by providing non-endogenous CETP molecules to an individual, for promoting an immune response tin such individuals against their endogenous CETP, thereby

demonstrates that as the level of CETP was increased in C57BL/6 mice -- HDL levels decreased while VLDL+LDL levels increased. Accordingly, we are not persuaded by the examiner's reliance on Marotti.

Similarly, it is our opinion that the examiner has misinterpreted the teachings of Breslow. According to Breslow (page 8316, column 2, second full paragraph), "CETP activity is lacking in mouse plasma. A human CETP minigene ... was used to make a transgenic line with human-like levels of [CETP] activity in plasma." Thus, in contrast to the claimed invention that requires the reduction of CETP levels, Breslow's CETP minigene mouse construct had an increased amount of CETP production. Accordingly, we are not persuaded by the examiner's reliance on Breslow.

The examiner relies on Stevens to support the assertion that

> since CETP is a "self" protein, it is not clear in the specification as filed how administering a whole recombinant human CETP ... would induce endogenous antibody direct[ed] toward one's own CETP at a level sufficient[ly] high to [break immune tolerance and thereby be effective in] modulat[ing] one's own level of endogenous CETP activity.

The examiner, however, has failed to provide any evidence to support the assertion that a non-endogenous CETP will be recognized as a "self" protein.[3] Further, the examiner failed to acknowledge or discuss appellants' disclosure (specification, pages 9-12) wherein appellants address both the use of multiple

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promoting a physiological condition (e.g., increased level of HDL or decreased level of LDL) correlated with a decreased risk of atherosclerosis."

[3] In this regard, we note that according to appellants' specification (page 15), "it was not known whether introduction of a non-endogenous CETP would be able to break tolerance in the subject

doses and the use of other techniques to enhance the immunogenicity of the CETP. Accordingly, we are not persuaded by the examiner's reliance on Stevens.

We remind the examiner that in order to satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph, a patent application must adequately disclose the claimed invention so as to enable a person skilled in the art to practice the invention at the time the application was filed without undue experimentation. Enzo Biochem, Inc. v. Calgene, Inc., 188 F.3d 1362, 1371-72, 52 USPQ2d 1129, 1136 (Fed. Cir. 1999). We note, however, that "nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples." In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). As set forth in In re Wright, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993):

> When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement.

On reflection, it is our opinion that the examiner failed to meet his burden of presenting the evidence necessary to support a finding of lack of enablement. Accordingly, we reverse the rejection of claims 40-48, 51

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vaccinated, leading to production of antibodies reactive not with (or not only with) the non-

and 52 under 35 U.S.C. § 112, first paragraph, as being based on an insufficient disclosure to enable the full scope of the claimed invention.

Written Description:

According to the examiner (Answer, page 9), notwithstanding polypeptides having SEQ ID NOs: 1, 3, 5 and 6, appellants' specification fails to provide an adequate "written description of any additional representative species of allelic variant of any human CETP such as any naturally occurring polymorphism as encompassed by the claims, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus."

The test for determining whether a claimed invention complies with the written description requirement of 35 U.S.C. § 112 is whether appellant has "convey[ed] with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). The examiner has the burden of establishing that the specification does not convey, with reasonable clarity, what is now claimed.

Here, appellants' specification discloses (page 2) that cholesteryl ester transport proteins (CETPs) are known in the art to mediate "the transfer of cholesteryl esters from HDL to TG-rich lipoproteins such as VLDL and LDL, and

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endogenous CETP but with the native CETP. These uncertainties have now been resolved."

also the reciprocal exchange of TG from VLDL to HDL...." More specifically, appellants' specification discloses (page 5),

> Non-endogenous CETP can be a non-endogenous allelic variation or polymorph of a mammalian CETP administered to the same species of mammal (e.g., a human CETP polymorph administered to another human); or the non-endogenous CETP can be a CETP from one species modified to have an amino acid sequence more similar to the native CETP of another species (e.g., a "humanized" rabbit CETP for administration to a human).[4]

Thus, it appears that the specification fully describs the claimed invention. Accordingly, it is incumbent on the examiner to explain why appellants' disclosure is insufficient to convey, with reasonable clarity to those skilled in the art that, as of the filing date sought, that appellants were in possession of the invention. Rather than providing such an explanation, the examiner simply asserts (Answer, page 19), "one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus." Therefore, in our opinion, the examiner has failed to meet his burden of establishing that appellants' specification fails to provide an adequate written description of the claimed invention. Accordingly, we reverse the rejection of claims 40-48, 51 and 52 under 35 U.S.C. § 112, first paragraph, that the specification that fails to adequately describe the claimed invention.

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[4] Appellants' further describe what is meant by "humanized" on pages 8-9 of their specification.

Anticipation:

According to appellants (Brief, page 7), "[w]ith respect to the grounds of rejection for anticipation ..., each of the appealed [c]laims 40, 41, 42, 43, 44, and 45 ... is separately patentable in view of Kwoh. Claims [47[5]], ... 51 and 52 ... will stand or fall together on the patentability of the base claims."

According to the examiner, claims 40-45, 47, 51 and 52 stand rejected under 35 U.S.C. § 102(a) as anticipated by Kwoh. Kwoh teach (abstract, accord page 2, lines 27-31), "[t]he present invention provides a method for increasing HDL cholesterol in a mammal by stimulating an immune response that inhibits the function of CETP. Such an immune response can be induced by immunizing with CETP or fragments of CETP (together termed 'CETP Peptides')...." Kwoh teach (page 4, lines 20-24), "CETP peptide[6] is administered to an appropriate individual in such a manner as to elicit an anti-CETP immune response."[7] As Kwoh explains (page 4, lines 14-19), this provides "an effective method of raising HDL in the blood or more specifically, the serum. By utilizing the body's own immune system to increase HDL levels...." In addition, we note that Kwoh teach

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[5] We note that appellants appear to have made a typographical error in the recitation of the claim groupings. Appellants include non-rejected claims 46 and 48, and exclude rejected claim 47 from the claim groupings. As we understand appellants' intended claim grouping, claims 47, "51 and 52 ... will stand or fall together on the patentability of the base claims."

[6] We emphasize that by use of the term "CETP peptide" in Kwoh refers to both "CETP or fragments of CETP." Kwoh, page 2, lines 27-31. See also, Kwoh (page 5, lines 11-14), "[a]s used herein, 'CETP peptide' is intended to include both the full length CETP amino acid sequence as well as fragments thereof."

[7] In this regard, we note that according to appellants' specification (page 9, lines 18-22), "[i]n practicing the methods of the present invention, non-endogenous CETP is administered to a mammal in an amount effective to elicit an immune response."

(page 5, lines 16-21), "[t]he peptides can have a sequence corresponding to or homologous to a mammalian CETP sequence. It will be appreciated that the peptide can differ from the native sequence to some extent so long as it is capable of inducing antibodies that inhibit the activity of CETP."

Appellant is correct (Brief, page 20, accord Reply Brief, page 6), "[u]nder 35 U.S.C. § 102, every limitation of a claim must identically appear in a single prior art reference for it to anticipate the claim." Gechter v. Davidson, 116 F.3d 1454, 1457, 43 USPQ2d 1030, 1032 (Fed. Cir. 1997). As we understand appellants' argument (Brief, pages 21-23, Reply Brief, pages 6-7), since Kwoh did not exemplify a method using a whole, non-endogenous CETP, the rejection must fall. We are not persuaded by this argument. A "reference must be evaluated for all it teaches and is not limited to its specific embodiments." The prior art is relevant for all it contains, including what it fairly suggests to one of ordinary skill in the art. In re Fracalossi, 681 F.2d 792, 794, n.1, 215 USPQ 569, 571, n.1 (CCPA 1982). Further, a reference need not have actually reduced the claimed invention to practice to be anticipatory. In re Sivaramakrishnan, 673 F.2d 1383, 1384-85, 213 USPQ 441, 442 (CCPA 1982). As discussed above, Kwoh teaches the administration to a mammal a whole, non-endogenous CETP. There is no evidence on this record that the whole, non-endogenous CETP taught by Kwoh is different than that claimed by appellants.

According to appellants' specification (page 8, lines 4-8), "[t]his invention is directed to the control of endogenous CETP activity by providing non-

endogenous CETP molecules to an individual, for promoting an immune response in such individual against their endogenous CETP, thereby promoting a physiological condition (e.g., increased level of HDL or decreased level of LDL)...." Similarly, Kwoh teach (page 2, lines 27-33), "a method for increasing HDL cholesterol in a mammal by stimulating an immune response that inhibits the function of CETP. Such an immune response can be induced by immunizing with CETP...." Thus, in our opinion the examiner has presented a prima facie case of anticipation. Accordingly, the burden of persuasion was properly shifted to appellants to show a lack of anticipation.

Appellants have not presented any probative evidence that the method taught by Kwoh is different from the method set forth in appellants' claims. Instead, appellants simply conclude (Reply Brief, page 6), Kwoh "do[es] not show any results from using a whole, non-endogenous CETP as specified in [a]ppellants' claims. Further, there are no results presented in Kwoh that anticipate or suggest the unexpected CETP activity, HDL-cholesterol levels, or LDL-cholesterol levels recited directly in the appealed claims." However, under the principles of inherency, after the PTO establishes a prima facie case of anticipation based on inherency, the burden shifts to appellant to "prove that the subject matter shown to be in the prior art does not possess the characteristic relied on." In re Crish, 393 F.3d 1253, 1258-60, 73 USPQ2d 1364, 1368-69 (Fed. Cir. 2004). Accord In re Swinehart, 439 F.2d 210, 212-13, 169 USPQ 226, 229 (CCPA 1971); In re Fitzgerald, 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980), quoted with approval in In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964,

966 (Fed. Cir. 1985); In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977); In re Ludtke, 441 F.2d 660, 664, 169 USPQ 563, 566 (1971). Accordingly, it is appellant's burden to demonstrate that the method taught by Kwoh does not result in:

- a reduction of CETP activity below 20% of that of the untreated mammal (appellants' claim 40);
- achieving a level of essentially 0 µg of CETP per milliliter of blood of the mammal (appellants' claim 41);
- achieving a lipoprotein profile wherein greater than about 90% of the total cholesterol in the blood of the mammal is HDL-cholesterol (appellants' claim 42);
- achieving a lipoprotein profile wherein about 100% of the total cholesterol in the blood of the mammal is HDL-cholesterol (appellants' claim 43);
- achieving a lipoprotein profile wherein less than 10% of the total cholesterol in the blood plasma of the mammal is LDL-cholesterol (appellants' claim 44); and
- achieving a lipoprotein profile wherein essentially none of the total cholesterol in the blood of the mammal is LDL-cholesterol (appellants' claim 45).

It is not sufficient to focus merely on Kwoh's examples, and the data reported therein, to the exclusion of what the entire Kwoh reference teaches. See e.g., Brief, pages 21-23. For the foregoing reasons, we find no error in the examiner's prima facie case of anticipation.

Accordingly, we affirm the rejection of claims 40-45, 47, 51 and 52 stand rejected under 35 U.S.C. § 102(a) as anticipated by Kwoh. As discussed above, claims 46, 47, 51 and 52 fall together with any one of claims 40-45.

OTHER ISSUES

Prior to the next Office Action, the examiner should take a step back and consider whether Kwoh, alone or in combination with another reference, would be considered prior art over claims 46 and 48 on appeal. If after having the opportunity to reconsider the record, the examiner is of the opinion that a rejection should be made, the examiner should issue an appropriate Office Action. We note, however, that any further communication from the examiner that contains a rejection of the claims should provide appellants with a full and fair opportunity to respond.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED-IN-PART

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